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RESISTANCE OF RENAL VESSELS IN HYPERTENSIVE PATIENTS TREATED WITH RESERPINE

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RESISTANCE OF RENAL VESSELS IN HYPERTENSIVE PATIENTS TREATED WITH RESERPINE

/Following is the translation of an article by N. S. Leont'yeva entitled "O Soprotivlenii Sosudov Pochek u Bol'nykh Gipertonicheskoy Bolezn'yu, Lechennykh Rezerpinom" (English version above) in Terapevticheskiy Arkhiv (Therapeutic Archives), Vol 32, No 5, Moscow, 1960, pages 12-18./

From the Chair of Propedeutics of Internal Diseases (Head -- Professor A. M. Damir) of the pediatric faculty of the Second Moscow Medical Institute imeni N. I. Pirogov

As is well known, a more or less uniform increase in the tone of the smooth musculature of arterioles, which in the late stages of the disease is combined with sclerotic changes in their walls, underlies the pathogenesis of hypertensive disease. This creates an increase in the resistance to blood flowing through the arterioles and leads to an impoverishment of the blood supply of organs and tissues of the body. Hence, the great interest which is presented by the study of the resistance of the bloodstream of

various organs and tissues in hypertensive disease and primarily the resistance of renal vessels is clear, since the disturbance of the circulation in them, occurring secondarily, becomes an important pathogenetic factor beginning with a definite period of the disease. In this connection, our attention has been attracted by the Gomez method, which makes it possible to study the resistance to the blood passing through the vessels of the entire kidney as well as through individual nephrons.

Poiseuille's law concerning the movement of fluids through capillary tubes underlies the Gomez method. It has been somewhat altered for application under conditions of movement of blood in small and very small arterioles of the living organism. In this modified form the Poiseuille's law attests to the fact that the peripheral resistance of the precapillaries is proportional to the average dynamic pressure and inversely proportional to the second volume of blood. Gomez, using this law in its application to the bloodstream of the kidneys, suggested calculating the total renal resistance R, the resistance of the afferent arterioles R_a, the resistance of the efferent arterioles R_E and veins of the kidneys R_v on the basis of the determination of the hydrostatic pressure in the renal blood vessels and the

volume of blood passing through them according to the following four formulas:

$$R = \frac{P_m - P_v}{Q} \times 1328; \quad (1)$$

$$R_a = \frac{P_m - P_g}{Q} \times 1328; \quad (2)$$

$$R_E = \frac{P_g - P_t}{Q - q} \times 1328; \quad (3)$$

$$R_v = \frac{P_t - P_v}{Q} \times 1328; \quad (4)$$

where P_m is the average arterial pressure of the renal artery in millimeters of mercury; P_v, the pressure in the renal vein in millimeters of mercury; P_g, the pressure in the glomerular capillaries in millimeters of mercury; P_t, the pressure in the peritubular capillaries in millimeters of mercury; Q, the renal blood flow in millimeters per second; q, the glomerular filtration in millimeters per second; 1328, the factor for converting pressure units into absolute resistance units -- dynes seconds/cm^{-5} (in the centimeter-gram-second system). (The physical system of measurement units in which length is measured in centimeters; mass, in grams; time, in seconds).

P_m, according to the data of experimental research, is equal to the mean pressure in the brachial artery, and is calculated

according to the following formula:

$$P_m = P_d + k(P_s - P_d),$$

where P_s is the systolic pressure; P_d the diastolic pressure; k, a factor which varies from 0.39 to 0.45, and, on the average, is equal to 0.42 according to Steinman's data.

P_v in people who are not suffering from signs of venous stasis, according to the experimental data of Maxwell and Breed, is equal to 10 millimeters of mercury.

Calculation of P_g is based on the principle that glomerular filtration is proportional to the difference between the mean glomerular pressure and the sum of the mean oncotic (h) and intracapsular pressure (H), multiplied by the permeability factor of the glomerular membrane (λ):

$$q = P_g - \lambda(h + H),$$

where λ = 0.0867; H, 10 millimeters of mercury; h, 25 millimeters of mercury.

P_v is practically equal to the sum of the oncotic and intracapsular pressures, because the pressure in the periglomerular capillaries is essentially equal to the oncotic and intracapsular pressures.

Therefore, for the purpose of calculating the resistance of the

renal blood vessels by the Gomez method it is essential to investigate the systolic and diastolic pressure in every patient, the renal circulation, and the glomerular filtration. Under hospital conditions this does not offer any great problem, in connection with which the determination of the renal resistance by the Gomez method is being used with progressively greater frequency in patients with hypertensive disease and has been approved by many clinicians.

Gomez, generalizing on the data of Bolomea and others, Corcoran, Taylor and Page, Maxwell and Breed, Fishman, presents the following average figures for the resistance of renal vessels as determined by these authors in 22 healthy persons: the total renal resistance, 6281 dynes/seconds/cm^{-5}; the resistance of afferent arterioles, 2005 dynes/seconds/cm^{-5}; the resistance of the efferent arterioles, 2258 dynes/seconds/cm^{-5}; and the resistance of the renal veins, 2240 dynes/seconds/cm^{-5}.

Kinney, Lawrence, Miller, Assali, and Duhring made a study of the renal resistance in patients with hypertensive disease and came to a conclusion that it is increased.

According to the data of Corcoran, Taylor and Page, the average value of the resistance of renal vessels which these authors

give is essentially different from the figure in healthy persons and is expressed by the following data: the total renal resistance is 16,730 dynes/second/cm^{-5}; the resistance of the afferent arterioles, 10,900 dynes/second/cm^{-5}; the resistance of the efferent arterioles, 2,520 dynes/second/cm^{-5}; the resistance of renal veins, 3,670 dynes/second/cm^{-5}.

These data attest to a considerable increase in the total renal resistance, chiefly because of an increase in the resistance of the afferent arterioles with a moderate increase in the resistance of the efferent arterioles and renal veins. A single investigation did not make it possible for these authors to determine what kind of changes of the renal blood vessels -- functional or organic -- serve as the cause of increase in the renal resistance.

In the Soviet literature we have succeeded in finding a single work, of S. K. Kiseleva, devoted to the study of the total renal resistance in patients with hypertensive disease.

The effect of pharmacologic agents used for the treatment of hypertensive disease is of special interest with respect to the resistance of the renal blood vessels. This problem has been analyzed in the works of Freis and others, Duhring and others,

Corcoran, MacKinnon, Lawson, Goldberg, Stover and others, et cetera.

Information concerning the condition of the resistance of renal vessels in patients with hypertensive disease when they are treated with reserpine, the most widespread and effective measure for therapy of this disease, is sparse. Thus, Reubi in three out of six patients with hypertensive disease and Moyer in two out of six patients with hypertensive disease noted a decrease in the total renal resistance; in others it was either unchanged or even increased somewhat.

S. K. Kiseleva found a decrease in the renal resistance in 24 out of 25 patients treated with rauwolfia preparations.

Information concerning the change in the resistance of afferent, efferent arterioles and renal veins in the treatment of patients with hypertension with reserpine could not be found in the foreign and Russian literature available to us. This stimulated us to make a study of the resistance of the entire renal bloodstream: the resistance of afferent, efferent arterioles and renal veins in patients with hypertensive disease given reserpine under hospital conditions.

There were 51 patients under our observation; of these, 34

were in the second stage and 17, in the third stage. There were 38 women; 13 men. In all patients, in addition to the usual careful clinical examination, a determination was made of the renal blood flow with diodrast using the Smith method in the Kireyev and Mishchenko modification, the glomerular filtration using endogenous creatinine without a water load by the Rehberg method, and the filtration fraction was calculated. The blood pressure at the time of the investigation amounted, on the average, to 179/108 millimeters of mercury in patients with stage II and 217/117 millimeters in patients with stage III of the disease. In 14 patients cardiovascular insufficiency, first degree, was found; six of them had had a myocardial infarction; in four patients, there was an organic disturbance of the cerebral circulation in the history.

A moderate albuminuria (0.03-1.5 grams per thousand) was found in 28 patients; hyposthenuria, in five. The nonprotein nitrogen in all patients was within normal limits.

Data concerning the condition of the renal hemodynamics before and after reserpine treatment are presented in Table 1.

As seen from Table 1 the renal plasma flow in the second stages of the disease was somewhat higher, on the average, than in

Table 1

Renal Hemodynamics in Hypertensive Patients before and after Reserpine Treatment

(1) Стадия болезни	(2) Момент исследования	(3) Число больных	(4) P_m в мм ртутного столба	(5) $60\,q$ в мл/мин	(6) $60\,Q$ в мл/мин	F	(7) $60\,Q$ в мл/мин	R	R_a	R_E	R_p
								(8) в дин/сек/см$^{-5}$			
II	(9) До лечения	34	139	73,7	371	0,22	675	16 448	11 065	2 256	3 168
	После лечения	34	112	77,1	541	0,17	984	9 398	5 619	1 652	2 265
	Процент изменения		19	5	31,4	22	31,4	42,8	49	26,8	29
III	(10) До лечения	17	153	93,7	355	0,29	648	20 260	14 725	2 828	3 370
	После лечения	17	130	81	431	0,21	783	13 840	9 774	2 201	2 851
	Процент изменения		15	13	21,7	27	21,7	31,7	33,6	22	15,4

(1) Stage of disease (2) Time of examination (3) No of pts. (4) P_m in mm of Hg (5) $60\,q$ in ml/min (6) $60\,Q$ in ml per min (7) $60\,Q$ in ml per min F R R_a R_E R_p (8) in dynes/second/cm^{-5}

II (9) Before treatment
After R_x
Percent change

III (10) Before R_x
After R_x
Percent change

stage III.

The glomerular filtration in individual patients varied from 32 to 188 cc/minute; the filtration fraction, from 0.06 to 0.58. The total renal resistance exceeded normal (6,281 dynes/second/cm^{-5}) by 2 1/2 times in the second stage and by 3 1/2 times in the third stage.

The resistance of the afferent arterioles was increased in a particularly marked fashion. In the second stage it exceeded normal (2,005 dynes/second/cm^{-5}) by 5 1/2 times; in the third stage, by seven times.

The resistance of the efferent arterioles proved to be unchanged in the second stage of the disease and was considerably increased in the third stage. The resistance of the renal veins

increased moderately.

As the result of a considerable increase in the resistance of the afferent arterioles the relationship of the resistance of afferent and efferent arterioles was changed. While in healthy people, according to Gomez, it amounts to 1:1.25, in our patients it was 4.9:1 in the second stage and 5.2:1 in the third stage.

The percentage distribution of the total renal resistance among its component parts was changed. While in healthy persons, as Smith reports, the resistance of the afferent and efferent arterioles and renal veins is approximately equal and 32-36 percent of the entire renal resistance is accounted for by the resistance of the afferent arterioles, in the patients whom we investigated the resistance of the afferent arterioles was increased to 68 percent in the second stage and 72 percent in the third stage. Our data coincide with the conclusions of Smith, who determined an increase in the resistance of afferent arterioles in patients with hypertensive disease up to 63-68 percent.

It is possible that the marked narrowing of afferent blood vessels accompanied by an increase in their resistance is, to a certain degree, of a "protective" nature (as Goldring believes), protecting the capillary network of the glomeruli from a marked

increase in pressure in them; however, in the final analysis this "protective mechanism" apparently proves to be the cause of ischemia of the renal tissue. This is confirmed by a comparison of the volume of the renal plasma flow and the total renal resistance, which depends, as have been mentioned above, chiefly on the resistance of the afferent arterioles. This comparison is illustrated by the data in Table 2.

Table 2

Distribution of Patients according to the Magnitudes of the Total Renal Resistance and the Volume of the Renal Plasma Flow

Renal plasma flow in cc/min	Total renal resistance in dynes/seconds/centimeters^{-5}		
	5,000-10,000	10,001-20,000	20,001-40000
	No of patients		
601 or higher	2	--	--
401-600	--	19	--
201-400		15	11
0-200		--	4

As is seen from Table 2, in two patients the renal resistance was normal or slightly increased, not exceeding 10,000 dynes/second/cm^{-5}, and the renal plasma flow was not disturbed. In 19 out of 34 patients with a considerable increase in the renal resistance (from 10,001 to 20,000 dynes/seconds/cm^{-5}) the volume of the renal plasma flow was reduced from 600 to

401 cc/minute, and in 15 patients, from 400 to 201 cc/minute. In all 15 patients the renal resistance of whom had been markedly increased (from 20,001 to 40,000 dynes/second/cm^{-5}), the renal plasma flow proved to be the lowest, varying from 157 to 395 cc/minute.

We began reserpine treatment after the stabilization of the arterial pressure on the fourth-sixth day that the patient was in the hospital. The preparation was given by mouth in a dose of 0.25-0.5 milligram per day with further increase in the dose to 0.75-one milligram; less often, to 1.25-1.5 milligram per day. On the average, the duration of treatment amounted to 22 days. Patients in the third stage were given a total of 18.1 milligrams; patients in the second stage, 15.8 milligrams of reserpine per course.

As a result of treatment the feeling of well being was improved in 46 patients, and the blood pressure decreased to varying degrees; in five patients the feeling of well being and the blood pressure did not change. On the average, the blood pressure decreased by 19 percent in the second stage and by 15 percent in the third stage of the disease, reaching, respectively, 149/85 and 173/98 millimeters of mercury. The renal plasma flow

increased to 541 cc/minute in the second stage and 431 cc/minute in the third stage (see Table 1). The glomerular filtration increased slightly in the second stage and decreased to 81 cc/minute in the third stage. The filtration fraction decreased to 0.17 in the second stage and 0.21 in the third stage of the disease.

The total renal resistance decreased in 48 patients, whereby the reduction was greater in the second stage. In 10 patients in the second stage the total renal resistance became normal; in one patient, it increased. The total renal resistance did not reach normal in a single patient in the third stage; in two patients it increased. The resistance of the afferent arterioles, despite a considerable reduction, even after treatment with reserpine, exceeded normal by 2 1/2 times in the second stage and by four times in the third stage of the disease and, as before, amounted to two-thirds of the total renal resistance. After treatment, the resistance of the efferent arterioles decreased; the resistance of the renal veins became normal.

Thus, under the influence of reserpine the resistance of the renal blood vessels decreased, as did also that of its constituent parts in the second and in the third stage of hypertensive disease, which is evidence of the great significance of functional changes

of renal blood vessels in the increase in their resistance.

Undoubtedly, organic changes of the renal blood vessels play a part in the increase in the renal resistance. This is confirmed by the fact that the renal resistance decreases to a lesser degree in the third, sclerotic stage of hypertensive disease, as well as by the higher level of resistance of the afferent arterioles specifically in those renal vessels in which, according to the data of I. V. Davydovskiy, A. I. Abrikosov and A. I. Strukov, and M. A. Zakhar'yevskaya, the organic changes develop sooner and to a more marked degree than in the other renal vessels which we studied.

A decrease in the renal resistance was always accompanied by an increase in the renal plasma flow. In all 10 patients in whom the renal resistance decreased to normal under the influence of reserpine the renal plasma flow increased to normal also. The increase in the renal resistance noted in three patients was associated with a reduction in the renal plasma flow.

The renal resistance decreases to a much greater extent than the blood pressure is reduced (see Table 1). This gives us the grounds for the supposition that the renal blood vessels are dilated more intensely than the extrarenal blood vessels. A

considerable increase in the renal plasma flow after treatment with reserpine confirms the correctness of this suggestion.

If we direct attention to the earlier occurrence of ischemia of the renal tissue which, according to the data of N. A. Ratner, P. M. Kireyev and others, occurs even in the first, functional stage of hypertensive disease, as well as to the great increase in renal resistance noted by Brod and others in patients with hypertension from pressor influences the impression is created that there is an increased reaction of renal blood vessels both to pressor and to depressor factors. It is possible that such a reaction of the renal blood vessels is one of the manifestations of a disturbance in the regulatory activity of the higher vasomotor centers.

Reserpine, which possesses a selective effect on these centers, restores or improves primarily the circulation of the kidneys, that is, of organs where it had been disturbed to a particularly considerable degree.

In comparing the values of glomerular filtration and the resistance of the individual renal blood vessels, we noted that glomerular filtration depends chiefly on the resistance of the renal arterioles. In those cases (11 patients before treatment and

five after treatment) where the resistance of the afferent arterioles increased to a particularly marked degree and exceeded the resistance of the efferent arterioles by 7 1/2-20 times, the glomerular filtration proved to be reduced to 34-60 cc/ minute. In those patients (12 patients before treatment and 13 after treatment) in whom the resistance of the afferent arterioles exceeded the resistance of the efferent arterioles by only 1 1/2-three times, the glomerular filtration was high -- from 90 to 188 cc/minute.

A change in the filtration fraction both before treatment (16 patients) and after treatment (33 patients) was explained chiefly by a disturbance in the renal circulation before reserpine treatment and its recovery during the course of treatment as a result of a change in the resistance of the renal blood vessels in the direction of an increase before treatment and decrease after treatment. Less often (five patients before treatment and 12 after treatment) the change in the filtration fraction was connected with the variation of the glomerular filtration as a result of the fact that the increase in resistance of the renal arterioles was different, as has been indicated above.

Conclusions

1. The total renal resistance, the resistance of the afferent, efferent arterioles and renal veins increases both in the second stage and in the third stage of hypertension, whereby this increase becomes greater with the progress of the disease.

2. The resistance of the afferent arterioles is increased in a particularly marked fashion and amounts to about two-thirds of the total renal resistance in patients with hypertensive disease instead of in one-third of the healthy persons.

3. The status of the renal circulation depends chiefly on the level of the renal resistance. It is worsened with the increase in the total renal resistance and improves when the latter is reduced.

4. Glomerular filtration depends chiefly on the ratio of the resistance of the afferent and efferent arterioles.

5. Functional as well as organic changes are of great importance in the increase in the resistance of renal blood vessels.

6. With reserpine treatment the renal resistance decreases against the background of reduction in the arterial pressure.

7. A considerable improvement in the renal circulation

under the influence of reserpine, because of the predominant dilatation of the renal arterioles, gives us the grounds for considering reserpine a most valuable pathogenetic agent in the treatment of patients with hypertension.

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